

What is claimed is:

1. A gene-targeted, non-human mammal heterozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), a human FAD Swedish mutation, and a humanized A β gene.

5

2. A gene-targeted, non-human mammal homozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), a human FAD Swedish mutation, and a humanized A β gene.

10 3. The mammal of claim 1 wherein said mutation of said PS-1 gene is P264L.

4. The mammal of claim 2 wherein said mutation of said PS-1 gene is P264L

5. The mammal of claim 1 wherein said mammal is a rodent.

15

6. The mammal of claim 5 wherein said mammal is a mouse.

7. The mammal of claim 2 wherein said mammal is a rodent.

20 8. The mammal of claim 7 wherein said mammal is a mouse.

9. Generational offspring of the mammal of claim 1 wherein said mutant PS-1 gene is expressed.

25 10. Generational offspring of the mammal of claim 2 wherein said mutant PS-1 gene is expressed.

11. A method for screening chemical compounds for the ability to decrease *in vivo* levels of A β peptide, said method comprising the steps of:

30 a) administering said chemical compound to the mammal of claim 1; and

b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

5 12. A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the mammal of claim 2; and

b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical
10 compound that has the ability to decrease *in vivo* levels of said A β peptide.

13. A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the mammal of claim 9; and

b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical
15 compound that has the ability to decrease *in vivo* levels of said A β peptide.

14. A method for screening chemical compounds for the ability to decrease *in vivo* levels of
20 the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the mammal of claim 10; and

b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical
25 compound that has the ability to decrease *in vivo* levels of said A β peptide.

15. The method of claim 11 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

16. The method of claim 12 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

17. The method of claim 13 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

18. The method of claim 14 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

19. A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

- a) administering a compound to the mammal of claim 1; and
- b) measuring the amount of A β peptide in a tissue sample from said mammal,

wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

20. A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

- a) administering a compound to the mammal of claim 2; and
- b) measuring the amount of A β peptide in a tissue sample from said mammal,

wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

21. A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

- a) administering a compound to the mammal of claim 9; and
- b) measuring the amount of A β peptide in a tissue sample from said mammal,

wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

22. A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

- a) administering a compound to the mammal of claim 10; and
- b) measuring the amount of A β peptide in a tissue sample from said mammal,

5 wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

23. The method of claim 19 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

24. The method of claim 20 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

25. The method of claim 21 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

26. The method of claim 22 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

27. A method of treating an individual suspected of having Alzheimer's disease comprising administering to said individual an effective Alzheimer's disease treatment amount of a compound identified by the method of claim 19.

28. A method of treating an individual suspected of having Alzheimer's disease comprising administering to said individual an effective Alzheimer's disease treatment amount of a compound identified by the method of claim 20.

29. A method of treating an individual suspected of having Alzheimer's disease comprising administering to said individual an effective Alzheimer's disease treatment amount of a compound identified by the method of claim 21.

30. A method of treating an individual suspected of having Alzheimer's disease comprising administering to said individual an effective Alzheimer's disease treatment amount of a compound identified by the method of claim 22.

5 31. A compound identified by the method of claim 11.

32. A compound identified by the method of claim 12.

33. A compound identified by the method of claim 13.

10

34. A compound identified by the method of claim 14.

35. A compound identified by the method of claim 19.

15

36. A compound identified by the method of claim 20.

37. A compound identified by the method of claim 21.

38. A compound identified by the method of claim 22.

20

Suba

39. A gene-targeted, non-human mammal heterozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), and a human transgenic for Swedish APP695.

25

40. A gene-targeted, non-human mammal homozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), and a human transgenic for Swedish APP695.

30

41. The mammal of claim 39 wherein said mutation of said PS-1 gene is P264L.

~~42. The mammal of claim 40 wherein said mutation of said PS-1 gene is P264E~~

43. The mammal of claim 39 wherein said mammal is a rodent.

~~44. The mammal of claim 43 wherein said mammal is a mouse.~~

45. The mammal of claim 40 wherein said mammal is a rodent.

46. The mammal of claim 45 wherein said mammal is a mouse.

47. Generational offspring of the mammal of claim 39 wherein said mutant PS-1 gene is expressed.

48. Generational offspring of the mammal of claim 40 wherein said mutant PS-1 gene is expressed.

49. A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the mammal of claim 39; and

b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

50. A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

a) administering said chemical compound to the mammal of claim 40; and

b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

51. A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

- a) administering said chemical compound to the mammal of claim 47; and
- b) measuring the amount of A β peptide in a tissue sample from said mammal,

5 wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

52. A method for screening chemical compounds for the ability to decrease *in vivo* levels of the A β peptide, said method comprising the steps of:

- a) administering said chemical compound to the mammal of claim 48; and
- b) measuring the amount of A β peptide in a tissue sample from said mammal,

10 wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said A β peptide.

15 53. The method of claim 49 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

54. The method of claim 50 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

20 55. The method of claim 51 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

56. The method of claim 52 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

57. A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

- a) administering a compound to the mammal of claim 39; and

b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

5 58. A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

a) administering a compound to the mammal of claim 40; and

10 b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

15 59. A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

a) administering a compound to the mammal of claim 47; and

15 b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

20 60. A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

a) administering a compound to the mammal of claim 48; and

25 b) measuring the amount of A β peptide in a tissue sample from said mammal, wherein a decrease in the amount of A β peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

61. The method of claim 57 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

62. The method of claim 58 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

63. The method of claim 59 wherein said tissue sample is selected from the group consisting
5 of brain tissue, non-brain tissue and body fluids.

64. The method of claim 60 wherein said tissue sample is selected from the group consisting of brain tissue, non-brain tissue and body fluids.

10 65. A method of treating an individual suspected of having Alzheimer's disease comprising administering to said individual an effective Alzheimer's disease treatment amount of a compound identified by the method of claim 57.

15 66. A method of treating an individual suspected of having Alzheimer's disease comprising administering to said individual an effective Alzheimer's disease treatment amount of a compound identified by the method of claim 58.

20 67. A method of treating an individual suspected of having Alzheimer's disease comprising administering to said individual an effective Alzheimer's disease treatment amount of a compound identified by the method of claim 59.

25 68. A method of treating an individual suspected of having Alzheimer's disease comprising administering to said individual an effective Alzheimer's disease treatment amount of a compound identified by the method of claim 60.

69. A compound identified by the method of claim 49.

70. A compound identified by the method of claim 50.

30 71. A compound identified by the method of claim 51.

72. A compound identified by the method of claim 52.

73. A compound identified by the method of claim 57.

5 74. A compound identified by the method of claim 58.

75. A compound identified by the method of claim 59.

76. A compound identified by the method of claim 60.

10

add a⁵⁷